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Design and Optimization of Chitosan-Based Microspheres for Sustained Delivery of Anastrozole

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ABSTRACT
The present study aimed to develop and evaluate Anastrozole-loaded mucoadhesive microspheres for sustained oral drug delivery using Sodium CMC, Chitosan, and HPMC K4M polymers. Microspheres were prepared by the solvent evaporation method and characterized for their micromeritic properties, percentage yield, drug entrapment efficiency, swelling behavior, mucoadhesion, surface morphology, and in vitro drug release. The prepared formulations exhibited satisfactory flow properties with particle sizes ranging from 420.15 to 468.41 µm. Percentage yield and drug entrapment efficiency were found to be in the ranges of 88.31–99.52% and 87.14–99.82%, respectively. The microspheres demonstrated excellent swelling and mucoadhesive characteristics, indicating their suitability for prolonged gastrointestinal residence. In vitro dissolution studies revealed sustained drug release for up to 12 h, with cumulative drug release ranging from 85.87% to 99.92%. Among all formulations, A6 containing Chitosan at a drug-to-polymer ratio of 1:2 showed the most desirable performance, achieving 99.92% drug release with superior mucoadhesion and controlled-release characteristics. FTIR studies confirmed the absence of significant drug–polymer interactions, while SEM analysis revealed discrete and spherical microspheres with smooth surface morphology. Drug release kinetic analysis demonstrated that the optimized formulation followed Zero-order kinetics with a non-Fickian diffusion mechanism. The findings suggest that Chitosan-based Anastrozole microspheres are a promising sustained-release oral delivery system capable of improving therapeutic efficacy and patient compliance in breast cancer management.

INTRODUCTION

Breast cancer remains one of the most frequently diagnosed cancers among women worldwide and continues to be a major cause of cancer-related mortality. Hormone receptor-positive breast cancer is commonly treated using endocrine therapy, which suppresses estrogen production and inhibits tumor growth [1]. Anastrozole, a non-steroidal aromatase inhibitor, is widely prescribed as a first-line therapy for postmenopausal women with hormone-dependent breast cancer. It acts by selectively inhibiting the aromatase enzyme responsible for converting androgens into estrogens, thereby reducing circulating estrogen levels and suppressing tumor progression [2]. Anastrozole possesses a molecular formula of $C_{17}H_{19}N_5$, a molecular weight of 293.37 g/mol, and an elimination half-life of approximately 40–50 hours. Despite its clinical effectiveness, conventional oral administration of Anastrozole may be associated with fluctuations in plasma drug concentration, frequent dosing requirements, and reduced patient compliance during long-term therapy [3]. Microsphere-based drug delivery systems have gained considerable attention as effective approaches for achieving controlled and sustained drug release. Microspheres are free-flowing spherical particles that can encapsulate therapeutic agents within a polymeric matrix, thereby protecting the drug and controlling its release profile [4]. Such systems offer several advantages, including prolonged drug release, enhanced bioavailability, reduced dosing frequency, minimized side effects, and improved patient adherence [5]. Among the various polymers employed in microsphere formulation, chitosan has emerged as a promising carrier because of its biocompatibility, biodegradability, mucoadhesive nature, and ability to enhance drug absorption across biological membranes. Studies have demonstrated that chitosan exhibits superior bioadhesive properties compared with conventional polymers such as starch, cellulose, and xanthan gum, resulting in prolonged gastrointestinal residence time and improved oral drug delivery [6]. Recent literature highlights the growing importance of chitosan-based microspheres in sustained drug delivery applications. Hema Jaiswal et al. (2024) reported that chitosan microspheres of Aceclofenac provided prolonged drug release, improved therapeutic effectiveness, and enhanced patient compliance compared with conventional dosage forms [7]. Similarly, P. Laxmi et al. (2024) developed Baricitinib-loaded microspheres that achieved controlled drug release for up

to 12 hours and demonstrated superior entrapment efficiency and bioavailability enhancement [8]. These findings suggest that microsphere technology offers significant advantages over traditional tablets and capsules by maintaining therapeutic drug concentrations for extended periods and reducing dosing frequency [9]. Although several controlled-release systems have been reported for various therapeutic agents, limited research has focused on the development of Anastrozole-loaded mucoadhesive microspheres for oral sustained delivery. Therefore, the present study was designed to formulate and evaluate Anastrozole-loaded microspheres using Sodium CMC, Chitosan, and HPMC K4M polymers by the solvent evaporation method [10]. The developed microspheres were characterized for particle size, flow properties, percentage yield, drug entrapment efficiency, swelling behavior, mucoadhesion, surface morphology, and in vitro drug release characteristics [11]. The objective was to develop a sustained-release oral delivery system capable of improving the therapeutic performance of Anastrozole while overcoming the limitations associated with conventional dosage forms. The use of chitosan-based microspheres is expected to provide enhanced mucoadhesion, prolonged gastrointestinal retention, improved drug utilization, and sustained drug release, thereby offering a promising strategy for the effective management of hormone-dependent breast cancer.

METHODOLOGY

Preparation of Standard Solutions

A stock solution of Anastrozole (1000 µg/mL) was prepared by dissolving 10 mg of drug in 10 mL methanol. A secondary stock solution (100 µg/mL) was prepared by diluting 1 mL of the stock solution to 10 mL with 0.1 N HCl (pH 1.2). Working standard solutions (5–25 µg/mL) were prepared by appropriate dilution and analyzed at 236 nm using a UV–Visible spectrophotometer. Calibration curves were established in 0.1 N HCl (pH 1.2), phosphate buffer pH 6.8, and phosphate buffer pH 7.4.

Preparation of Anastrozole Microspheres

Anastrozole-loaded microspheres were prepared by the solvent evaporation technique using Sodium CMC, Chitosan, and HPMC K4M as polymers. The drug and polymers were dissolved in a dichloromethane: methanol mixture and dispersed into 100 mL of 0.2% w/v light liquid paraffin under continuous stirring at 250 rpm. After solvent evaporation, the formed microspheres were collected, washed with purified water, dried at room temperature, and stored in a desiccator for further studies.

Evaluation of Microspheres

The prepared microspheres were evaluated for bulk density, tapped density, Carr's compressibility index, Hausner ratio, angle of repose, percentage yield, drug entrapment efficiency, and swelling index using standard procedures. Drug entrapment efficiency was determined by extracting the drug from microspheres in phosphate buffer pH 7.4 and analyzing the samples at 236 nm.

In Vitro Drug Release Study

In vitro drug release studies were carried out using USP Type I dissolution apparatus at 37 ± 0.5°C and 50 rpm. Microspheres equivalent to 100 mg of Anastrozole were subjected to dissolution in simulated gastric fluid (pH 1.2) for 2 h, phosphate buffer pH 6.8 for 3 h, followed by phosphate buffer pH 7.4. Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically at 236 nm, replacing an equal volume of fresh dissolution medium after each sampling.

Drug Release Kinetics

The release data were fitted to Zero-order, First-order, Higuchi, and Korsmeyer–Peppas kinetic models to determine the mechanism of drug release and release kinetics.

FTIR Analysis

Fourier Transform Infrared (FTIR) spectroscopy was performed to evaluate possible drug–polymer interactions. Samples were prepared using the potassium bromide pellet method and scanned over the range of 4000–500 cm^{-1}.

Scanning Electron Microscopy (SEM)

The surface morphology of the optimized microspheres was examined using Scanning Electron Microscopy (SEM). Samples were mounted on aluminium stubs, gold coated and observed under suitable magnifications to assess particle shape and surface characteristics.

RESULTS AND DISCUSSION

UV Spectroscopic Analysis

Anastrozole exhibited a maximum absorbance (λmax) at 236 nm in both simulated gastric fluid (pH 1.2) and phosphate buffer (pH 7.4). Calibration curves showed excellent linearity within the concentration range of 5–25 µg/mL. The regression coefficients (R^2) were 0.9998 and 0.9999 in pH 1.2 and pH 7.4 media, respectively, confirming the suitability of the analytical method for quantitative estimation of Anastrozole.

Micromeritic Properties of Microspheres

The prepared microspheres exhibited mean particle sizes ranging from 420.15 to 468.41 µm. An increase in polymer concentration resulted in larger particle sizes due to increased viscosity of the dispersed phase. Bulk density and tapped density values ranged from 0.377–0.725 g/cm^3 and 0.412–0.933 g/cm^3, respectively. Hausner ratio (1.195–1.433), Carr's index (9.69–26.00%), and angle of repose (<30°) indicated acceptable flow properties of all formulations

Percentage Yield and Entrapment Efficiency

The percentage yield of microspheres ranged from 88.31% to 99.52%, indicating efficient recovery of the prepared formulations. Drug entrapment efficiency varied between 87.14% and 99.82%. Higher polymer concentrations resulted in increased drug entrapment, possibly due to enhanced matrix formation and reduced drug diffusion into the external phase during preparation. Formulation A9 exhibited the highest entrapment efficiency (99.82%), while formulation A5 showed 99.45% entrapment efficiency.

Swelling Behavior

The swelling index of the microspheres ranged from 77.29% to 96.02%. Polymer concentration significantly influenced the swelling characteristics of the microspheres. Increased polymer content enhanced water uptake and swelling capacity, which is advantageous for sustaining drug release and improving mucoadhesion. The highest swelling index was observed for formulation A2 (96.02%).

Mucoadhesion Study

The prepared microspheres demonstrated satisfactory mucoadhesive properties. Mucoadhesion values ranged from 71% to 96% depending on the polymer type and concentration.

Chitosan- and HPMC K4M-based formulations exhibited superior mucoadhesion compared to Sodium CMC formulations, attributable to stronger interactions between the polymer and mucosal surface. Formulation A8 showed the highest Mucoadhesion value (96%).

In Vitro Drug Release Study

All formulations exhibited sustained drug release over a period of 12 h. Drug release was influenced by polymer type and concentration. The cumulative drug release after 12 h ranged from 85.87% to 99.92%. Among all formulations, A6 demonstrated the highest cumulative drug release (99.92%) at 12 h, followed by A9 (97.53%) and A5 (97.12%). The sustained release behavior can be attributed to the formation of a polymeric matrix that prolonged drug diffusion and release.

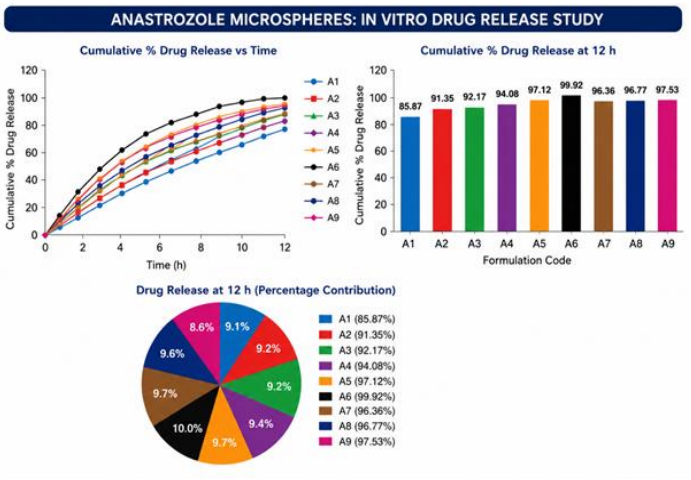

Figure.1: In-vitro drug release data of Anastrozole microspheres

Drug Release Kinetics

The optimized formulation was subjected to kinetic modeling using Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models. The release profile showed the highest correlation with the Zero-order kinetic model (R^2 = 0.9932), indicating a constant drug release rate. The Peppas release exponent suggested a non-Fickian diffusion mechanism, indicating that drug release occurred through a combination of diffusion and polymer relaxation/erosion processes.

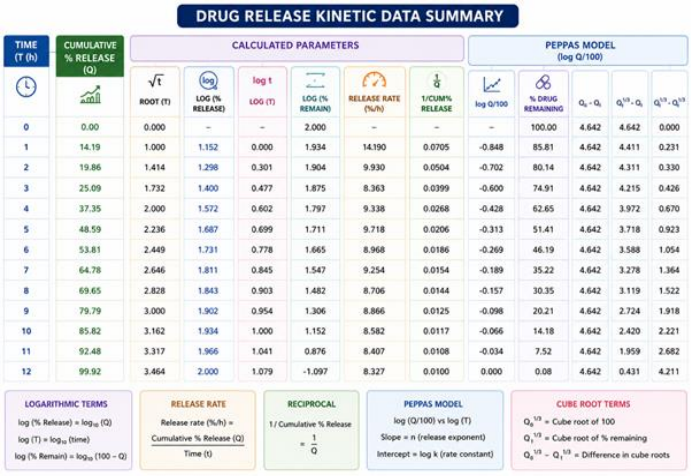

Figure.2: Release kinetics studies of the optimized formulation (A6)

FTIR Analysis

FTIR spectra of the optimized formulation were compared with those of pure Anastrozole. The characteristic peaks of the drug were retained without significant shifts or disappearance, indicating the absence of any chemical interaction between Anastrozole and the selected polymers.

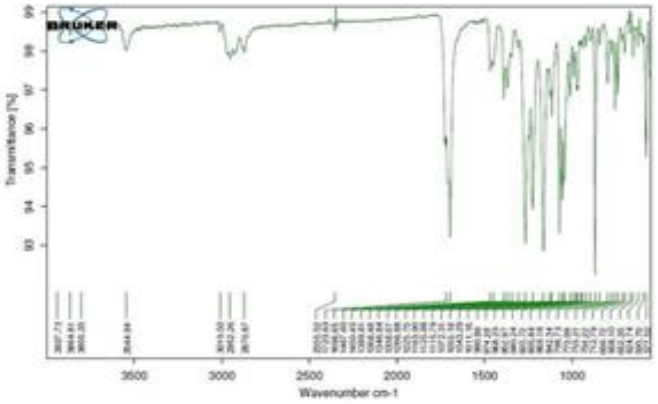

Figure.3: FTIR of Pure Drug

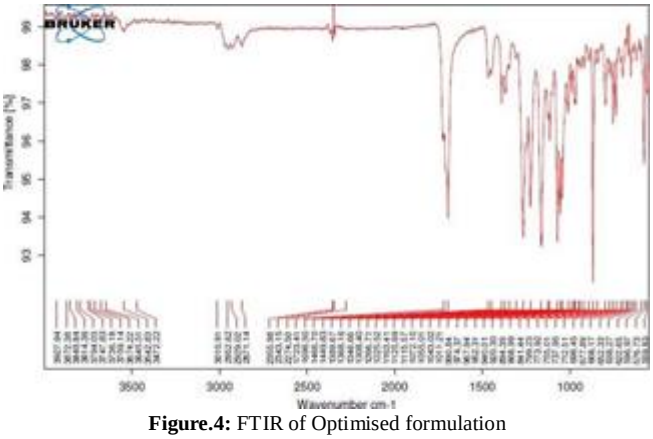

Figure.4: FTIR of Optimised formulation

Scanning Electron Microscopy (SEM)

SEM analysis revealed that the prepared microspheres were discrete, spherical, and exhibited a relatively smooth surface morphology. The results confirmed successful formation of microspheres by the solvent evaporation method and supported the sustained-release characteristics observed during dissolution studies.

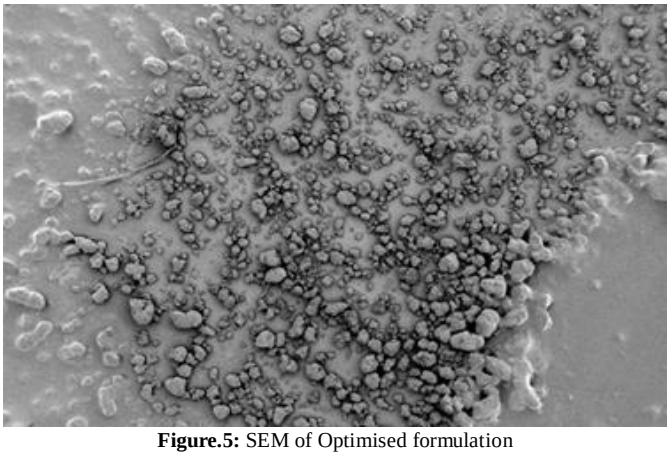

Figure.5: SEM of Optimised formulation

Optimization of Formulation

Among all formulations, A6 containing Chitosan demonstrated the most desirable balance of drug entrapment efficiency, muco adhesion, and sustained drug release characteristics. The formulation achieved nearly complete drug release (99.92%) over 12 h and followed Zero-order release kinetics with a non-Fiskian diffusion mechanism, making it a promising candidate for oral sustained-release delivery of Anastrozole.

Table .1: Calibration curve data for Anastrozole in Simulated gastric fluid pH 1.2 and pH 7.4 Phosphate Buffer

Concentration (µg/ml)	Absorbance (pH 1.2)	Concentration (µg/ml)	Absorbance (pH 7.5)
0	0	0	0
5	0.107	5	0.122
10	0.215	10	0.241
15	0.321	15	0.364
20	0.421	20	0.481
25	0.535	25	0.598

Table 2: Micro Metric Property of Microspheres of Anastrozole

Formulation code	Mean particle size	Bulk density ((gm./cm^3))	Tapped density (gm./cm^3)	Hauseners ratio	Carr's index	Angle of repose
A1	451.54	0.655±0.1	0.814±0.1	1.385	23.22	27.6 ± 0.2
A2	442.69	0.484±0.4	0.534±0.3	1.230	12.53	27.0 ± 0.3
A3	435.14	0.516±0.2	0.576±0.3	1.242	13.50	27.7 ± 0.4
A4	451.65	0.576±0.3	0.626±0.2	1.205	8.52	26.1 ± 0.1
A5	430.96	0.725±0.1	0.933±0.1	1.433	26.00	29.3 ± 0.4
A6	420.15	0.621±0.3	0.731±0.3	1.221	18.39	25.4 ± 0.4
A7	468.41	0.688±0.3	0.766±0.4	1.433	12.76	28.1 ± 0.1
A8	431.95	0.377±0.2	0.412±0.2	1.233	12.11	26.2 ± 0.1
A9	422.14	0.534±0.2	0.576±0.3	1.195	9.695	24.2 ± 0.2

Table 3: Percentage yield and percentage drug entrapment efficiency of the prepared microspheres

S.No	Formulation code	%Yield	Drug Content (mg)	%Drug entrapment efficiency
1	A1	88.31	97.14	87.14
2	A2	92.12	99.65	91.91
3	A3	97.08	99.76	92.72
4	A4	91.74	99.14	96.58
5	A5	97.91	97.52	99.45
6	A6	98.24	100.04	94.87
7	A7	97.39	98.24	89.72
8	A8	99.52	99.53	93.51
9	A9	99.47	99.21	99.82

Table 4: Swelling studies

S.No	Formulation	Initial	Final	Percentage
1	A1	10	13.45	90.32
2	A2	10	12.62	96.02
3	A3	10	14.58	83.63
4	A4	10	13.45	90.32
5	A5	10	14.95	81.68
6	A6	10	15.86	77.29
7	A7	10	11.59	94.42
8	A8	10	12.75	95.10
9	A9	10	13.96	87.16

Table.5: In-Vitro Mucoadhesion Test of all Formulations

S.No	Formulation Code	No.of microspheres		Percentage Mucoadhesion
		Initial	Final	
1	A1	20	16.48	71
2	A2	20	12.85	78
3	A3	20	16.14	80
4	A4	20	18.96	93
5	A5	20	21.71	95
6	A6	20	17.17	85
7	A7	20	17.80	93
8	A8	20	12.58	96
9	A9	20	18.21	88

CONCLUSION

Anastrozole-loaded microspheres were successfully developed using the solvent evaporation method employing Sodium CMC, Chitosan, HPMC K4M polymers. The prepared formulations exhibited satisfactory micromeritic properties, with particle sizes ranging from 420.15 to 468.41 µm and acceptable flow characteristics. Drug entrapment efficiency ranged from 87.14% to 99.82%, while percentage yield varied between 88.31% and 99.52%, demonstrating the efficiency and reproducibility of the preparation method. Swelling studies and mucoadhesion evaluation confirmed the ability of the microspheres to retain their integrity and adhere effectively to mucosal surfaces, thereby enhancing gastrointestinal residence time. In vitro dissolution studies revealed sustained drug release for up to 12 hours, with cumulative drug release ranging from 85.87% to 99.92%. Among all formulations, A6 showed the most desirable performance, achieving 99.92% drug release over 12 hours with excellent mucoadhesive properties and controlled-release behavior. FTIR studies confirmed the absence of significant drug–polymer interactions, while SEM analysis demonstrated the formation of discrete, spherical microspheres with smooth surface morphology. Drug release kinetic analysis indicated that the optimized formulation followed Zero-order kinetics with a non-Fickian diffusion mechanism, suggesting a combined effect of diffusion and polymer relaxation on drug release. Overall, the developed Chitosan-based microspheres, particularly formulation A6 with a drug-to-polymer ratio of 1:2, represent a promising oral sustained-release delivery system for Anastrozole. The formulation demonstrated outstanding muco adhesivity, high drug entrapment efficiency, satisfactory yield, and prolonged drug release. These findings suggest that Anastrozole-loaded Chitosan microspheres could effectively overcome the bioavailability limitations associated with conventional dosage forms and provide improved therapeutic efficacy through sustained oral drug delivery.

CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

FUNDING: This study received no specific funding from public, commercial, or not-for-profit funding agencies.

AI TOOL DECLARATION

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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